## REMARKS

Claims 1-39 and 95-98 are pending and rejected. Claims 40-94 have been canceled without prejudice and were withdrawn from examination due to a restriction requirement. Applicants reserve their right to prosecute subject matter of cancelled claims in subsequent applications.

Claims 1 and 28 have been amended to recite a method for constructing a nucleic acid library comprising where step c) is digesting said first portion with at least one sequence-specific endonuclease wherein said first portion is divided into one pool per endonuclease;

d) digesting said second portion with at least one (Y) endonuclease having a degenerate recognition sequence and fractionating the digested cDNA into $YX^z$ pools where Y is the number of degenerate endonucleases, X is the the extent of degeneracy and z is the number of bases;

e) isolating nucleic acid fragments from said endonuclease digestions of said first and second portions using said end-labels;

f) digesting the fragments of said first portion with said at least one endonuclease of d) sequence and fractionating the digested cDNA into $YX^z$ pools where Y is the number of degenerate endonucleases, X is the the extent of degeneracy and z is the number of bases;

g) digesting the fragments of said second portion with said at least one endonuclease of c) wherein the second portion pools are divided into one pool per endonuclease;

h) removing labeled nucleic acid fragments from said first and second portions while retaining unlabeled fragments;

i) adding a population of adapters to each of the pools, said population containing adapters specific for the endonucleases used, wherein each adapter comprises a first region specific to a particular endonuclease used and a second region containing a primer binding site.

Claim 95 has been amended to recite a method for constructing a nucleic acid library comprising:

a) obtaining a population of double stranded cDNA wherein cDNA molecules contained in said population contain a detectable label on their 3' end;

b) digesting said double-stranded cDNA with at least one restriction endonuclease having a degenerate recognition sequence comprising at least one

degenerate base, wherein said digestion creates a single-stranded portion or overhang containing a region having the formula $N^m$, where N is the extent of degeneracy and m is the number of degenerate bases in said single stranded portion or overhang to produce digestion fragments and fractionating the digested cDNA into $YX^z$ pools where Y is the number of degenerate endonucleases, X is the extent of degeneracy and z is the number of bases ;

c) adding a population of adapters to each of the pools, said adapters specific for the at least one endonuclease used;

d) hybridizing and ligating said adapters to the 5' end of said digestions fragments;

e) separating said 3' end digestion fragments using said detectable label;

f) amplifying said 3' end digestion fragments;

g) separating said amplified digestion fragments on the basis of size.

Support for these amendments is in the specification on pages 19-20 and Example 1.

No new matter has been added by these amendments.

**Affirmation of Election**

Applicants affirm the telephone election with traverse, to elect the invention of Group I, claims 1-39 and 95-98.

**Claims rejections under 35 USC §103**

A. Claims 1-4, 6-7, 9-18, 20, 21, 26-30, 34-36 and 95-97 are rejected under 35 USC § 103(a) as allegedly obvious over Warthoe (WO 98/51789) in view of Marshall et al. (US 5,420,032). In particular, the Office Action alleges that "an ordinary practitioner would have been motivated to combine and substitute a method of digesting nucleic acid molecules with an endonuclease having a degenerate recognition sequence of Marshall into the method of Warthoe. . . ."

Applicants respectfully disagree with this rejection.

A finding of obviousness under § 103 requires a determination of the scope and content of the prior art, the level of ordinary skill in the art, the differences between the claimed subject matter and the prior art, and whether the differences are such that the subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. Graham v. Deere, 383

U.S. 1 (1966). The relevant inquiry is whether the prior art suggest the invention, and whether the prior art provides one of ordinary skill in the art with a reasonable expectation of success. In re O'Farrell 853 F.2d 894, 903 (Fed. Cir. 1988). Both the suggestion and the reasonable expectation of success must be founded in the prior art and not in the Applicants' disclosure. In re Vaeck 947 F.2d 488 (Fed. Cir. 1991).

The cited references do not make obvious the presently claimed invention.

The presently claimed invention describes and teaches a method of constructing a nucleic acid library which comprises a step d) of digesting said second portion with at least one endonuclease having a degenerate recognition sequence and in which the portions are divided into pools equal to the number of specific endonucleases used and fractionated into the number of pools equal to the number of degenerate cut sites ($YX^z$).

Warthoe et al. does not describe, nor teach, that a second portion of labeled polynucleotides should be digested with at least one endonuclease with a degenerate recognition sequence. On pages 15-16, as pointed out in the office action, merely states a second restriction enzyme could be used, such as a 4-base cutter, which statistically cleaves at least 50% of said sub-fragments. Further, Warthoe does not describe construction of a non-redundant library where the cDNA is divided into the number of specific endonucleases times the number of degenerate cut sites.

Marshall et al. describe an endonuclease I-CeuI that recognizes a non-symmetric degenerate sequence (col.5-6). The I-CeuI enzyme "generates from the 5' end of the upper strand a cut after the tenth nucleotide for the 15 nucleotide sequences or after the twelfth nucleotide for the 17 and 19 nucleotide sequences, and from the 5' end of the lower strand after the ninth nucleotide for the 15 and 17 nucleotide sequences or after the eleventh nucleotide for the 19 nucleotide sequences, thereby generating a 4 nucleotide extension with a 3'OH overhang." (col. 7, lines 6-12).

Therefore, Warthoe in view of Marshall do not teach, much less suggest, the presently claimed invention. Thus, the present invention is not obvious.

B. Claims 23-25 and 37-39 are rejected under 35 USC § 103(a) over Warthoe in view of Marshall and further in view of Oliner et al. (US 6,340,565). In particular, the Office Action alleges that it would have been obvious to combine and substitute a

method, wherein isolating and removing of end-labeled nucleic acid molecules is by particles that bind the end-labeled nucleic acid molecules and wherein the label and the particles are biotin and streptavidin of Oliner into the method of Warthoe in view of Marshall in order to improve the analysis of a plurality of target nucleic acid.

Applicants respectfully disagree with this rejection.

Applicants arguments against Warthoe and Marshall are above in section A. Oliner merely describes a method of isolating and separating end-labeled nucleic acids using particles and biotin/streptavidin.

Oliner does not suggest the presently claimed method as described above, and does not add the teachings lacking in Warthoe and Marshall. Therefore, since Warthoe in view of Marshall and Oliner do not teach, much less suggest, the present invention. The cited references alone or in combination do not make the presently claimed invention obvious.

C. Claims 5, 19 and 31 are rejected under 35 USC § 103(a) over Warthoe in view of Marshall et al., further in view of Fox et al. (US 6,140,086). In particular, the Office Action alleges that it would have been obvious to combine and substitute the method, wherein the at least one specific endonuclease is selected from the group consisting of EcoRI, HindIII, BamHI, NcoI, and XhoI of Fox into the method of Warthoe in view of Marshall.

Applicants respectfully disagree with this rejection.

Applicants arguments against Warthoe and Marshall are set forth in section A. Fox merely describes methods for cloning nucleic acid molecules where at least one endonuclease is selected from a list of endonucleases including EcoRI, HindIII, BamHI, NcoI, and XhoI.

Fox does not suggest the presently claimed method as described above, and does not add the teachings lacking in Warthoe and Marshall. Therefore, since Warthoe in view of Marshall and Fox do not teach, much less suggest, the present invention. The cited references alone or in combination do not make the presently claimed invention obvious.

D. Claims 8,22, 32, and 98 are rejected under 35 USC § 103(a) over Warthoe in view of Marshall further in view of Jones et al. (US 6,372,479). In particular, the Office Action alleges it would have been obvious to combine and substitute a

method, wherein at least one endonuclease having a degenerate recognition sequence is Bsl I of Jones et al.

Applicants respectfully disagree with this rejection.

Applicants arguments against Warthoe and Marshall are set forth in section A above.

Jones merely describes a method of cloning DNA using at least one endonuclease BsII.

Jones does not suggest the presently claimed method as described above, and does not add the teachings lacking in Warthoe and Marshall. Therefore, since Warthoe in view of Marshall and Jones do not teach, much less suggest, the present invention. The cited references alone or in combination do not make the presently claimed invention obvious.

E. Claim 33 is rejected under 35 USC § 103(a) as allegedly obvious over Warthoe in view of Marshall , further in view of Fox., and further in view of Jones et al. In particular, the Office Action alleges that it would have been obvious to combine and substitute a method, wherein at least one endonuclease having a degenerate recognition sequence is Bsl I of Jones, into a method of Warthoe in view of Marshall, further in view of Fox. to achieve the express advantages, as noted by Jones et al, of preferred restriction sites including Bsl I, which generates 3' cohesive ends with overhangs having a length of 3 nucleotides.

Applicants respectfully disagree with this rejection.

Applicants arguments against Warthoe and Marshall are set forth above in section A. Applicants arguments against Fox are set forth in section C, and arguments against Jones are set forth in section D.

Again, alone or in combination, Warthoe, Marshall, Fox and Jones, does not teach, much less suggest, the presently claimed invention. Therefore, the presently claimed invention is not obvious.

The above arguments and amendments overcome the rejections, and Applicants respectfully request their withdrawal.

Respectfully Submitted,

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